fig. 1a: Observed (green) and predicted (red) cumulative incidence of grade 2+ esophagitis versus the V50Gy in the esophagus.

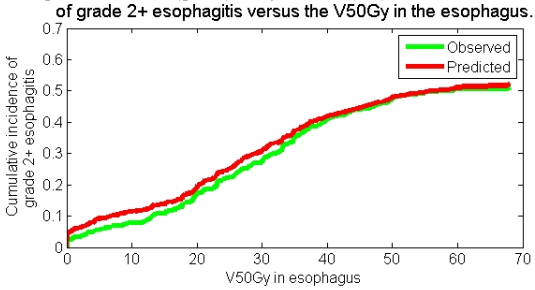
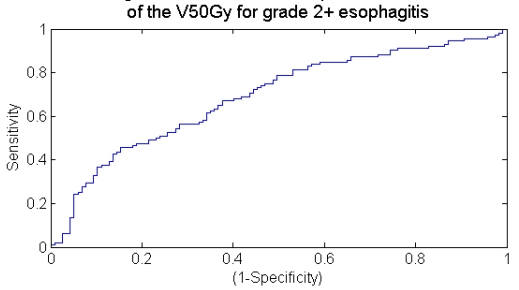


fig. 1b: ROC curve for the predictive value of the V50Gy for grade 2+ esophagitis



Conclusion: The observed and predicted dose-effect of grade ≥2 esophagitis were almost identical. This implies that our esophagus dose parameter accurately predicts toxicity for our current patient population and treatment protocol. This result is surprising, since esophagitis incidence was expected to decrease because of the introduced pre-hydration. While the origin of this discrepancy requires further investigation, it does show that the electronic toxicity scoring system and connection to the dose parameters appears to be a useful and valuable tool to audit the applicability of dose constraints in daily clinical practice.

EP-1717

Impact of radiation induced cell death kinetics on reoxygenation and tumour response.

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Purpose or Objective: The radiosensitivity of cells has an oxygen dependence that leads to an undesired resistance of hypoxic tumour cells. This is well known[1] and the linear quadratic response model has been extended to account for it.[2] In order to properly model tumour responses, the information about the distribution of oxygen at a microscopic scale must be available.[3] Modelling works usually derive this distribution by solving the reaction-diffusion equation in a voxelized tumour geometry that includes a vascularization distribution model.[4] However, the oxygen available to the cells increases during radiotherapy due to, among other factors, cell killing. This reoxygenation process can turn hypoxic cells into oxic, changing the cells radiosensitivity during the treatment. In this work we implement two models of cell death kinetics, CDKM, to analyse how they affect reoxygenation and hence the response of tumours to radiotherapy.

Material and Methods: Two CDKMs are compared:
a) Delayed cell killing model, DCDKM: The number of dead cells after irradiation varies with time according to an exponential expression. Cells can die shortly or long after irradiation, mimicking early and late apoptosis.
b) Instantaneous cell killing model, ICDKM: Cell death occurs immediately after irradiation (early apoptosis scenario).
Using these models, oxygen distributions are recomputed before the delivery of each fraction, considering the decrease in oxygen consumption due to cell death caused during the previous fractions. The oxygen consumption can be computed globally, by voxel averaging surviving fractions, or locally, at a subvoxel scale. The differences in reoxygenation and tumour response arising under different CDKM and oxygen consumption scenarios depend on the vascular fraction, VF, and the fractionation scheme. This was illustrated for a conventional schedule and a hypofractionated treatment.

Results: In the conventional treatment, the doses needed to achieve 50% tumour control (D50) are ~ 10 and 2 Gy larger under the ICDKM (for VFs of 1% and 3%, respectively). Differences are larger in the hypofractionated scheme, for which the TCP remains equal to zero under the DCDKM for a VF equal to 1%. For a VF equal to 3%, D50 values are ~ 20 Gy larger under the DCDKM. Similar results were found under the global and local oxygen consumption calculations.

Conclusion: This work shows that the kinetics of cell death can have a great impact in the simulation of reoxygenation and tumour response. Radiation response models should account for cell death kinetics to properly evaluate tumour response, especially in hypofractionated schemes.

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EP-1718

Estimation of tumor radio-sensitivity using mathematical models and analysis of the oxygenation role

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Purpose or Objective: The project aims at predicting tumor radiation starting from pre-treatment information related to cancer volume and oxygenation.

Material and Methods: Eighteen Copenhagen rats, implanted with prostate tumor, underwent two irradiations (2x15Gy). Nine rats were treated in standard conditions (Air), while the remaining group (Oxy) inhaled oxygen. Before the first irradiation, an interleaved blood (BOLD) and tissue (TOLD) oxygen level dependent (IBT) MRI sequence was performed. Four indices were computed, namely, BOLD and TOLD signal intensity variation (dSI), and the change in longitudinal (dR1) and transverse (dR2*) relaxation rate. The tumor volume evolution was monitored by means of weekly caliper measurements. A two-equation system describing the uncontrolled growth and the response to treatment of the active cells population, along with the dead cell clearance dynamics, was implemented in Matlab® (MathWorks, Natick, Massachusetts, USA). Three parameters, namely the volume doubling time, the radiation sensitivity (α) and the dead cell clearance time, were learned on a subject-specific basis using a genetic algorithm. Finally, a feed forward neural network (FF-ANN) was trained (*Fig. 1*) to predict α starting from the MRI indices and initial volume, for each group (Air/Oxy).

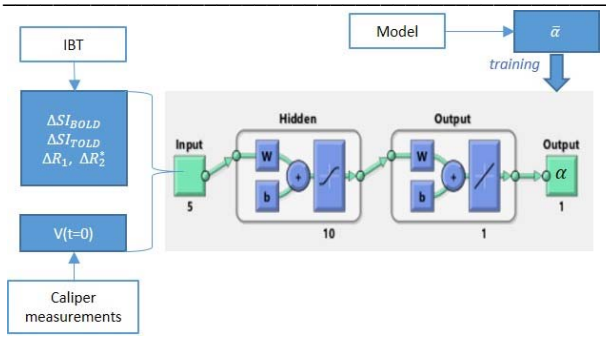

Fig 1. FF-ANN scheme.

Results: An inverse correlation of the radio-sensitivity parameter assessed by the model was found with respect the dR2* (-0.65) for the Oxy group. A further subdivision according to positive and negative values of dR2* showed a larger average radio-sensitivity for the Oxy rats with <0 and a significant difference in the two distributions according to the Wilcoxon-Mann-Whitney test ($p<0.05$). Finally, the Pearson correlation coefficient ($R^2>0.9$) revealed a strong agreement of the FF-ANN output with the target radio-sensitivity.

Conclusion: These preliminary findings support the hypothesis that the change in the R2* can be related to tumor oxygenation and, consequently, to its radio-sensitivity. In particular, the sign of the tendency is in accordance with the fact that an oxygenation increase reduces the tumor relaxation rate as reported in the literature. Moreover, the different distributions of α, outlined in the Oxy subgroups according to the dR2*, suggest that some subjects would benefit from oxygen inhalation more than others, reasonably due to their initial vascularization. Finally, the performance of the FF-ANN is promising, although it would require a larger dataset to validate its prediction ability.

EP-1719

Radiobiology based head & neck cancer protocol (FAMOSO) combining accelerated RT and EGFr inhibitor

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Purpose or Objective: Administration of monoclonal antibody Epidermal Growth Factor Receptor (MoAb-EGFr) inhibitor every week during Radiotherapy (RT) of head and neck cancer (HNC) has shown improved outcomes as compared to RT alone in terms of locoregional disease control, progression free and overall survival, thanks to its radiosensitizing effect. MoAb-EGFr concentration varies day by day after injection, and radiosensitizing effect accordingly. A radiobiological (RB) model accounting for this variation (Pedicini, et al. Radiat Oncol. 2012;7:143) can be applied to shorten the treatment by optimizing daily RT dose, still maintaining unchanged the biological effect on the tumour (in terms of surviving cells) as compared to standard RT (7 weeks, PTV1: GTV, 70Gy; PTV2 = GTV+margin, 63Gy; PTV3: lymph nodes: 58.1Gy) and potentially reducing healthy tissue toxicity. In this study, such RB model was adopted in the clinical protocol FAMOSO (Frazionamento Accelerato MOdulato in SIB-IMRT dei tumori testa-collO) for the treatment of HNC tumours with simultaneous integrated boost (SIB), aiming to test the feasibility of accelerated modulated fractioning and to assess toxicity and response rate.

Material and Methods: From literature data, showing that higher concentrations of MoAb-EGFr correspond to steeper tumor cell survival curves, radiobiological parameters were derived and included in the RB model to obtain the daily dose to be delivered to each target volume. To date, 2 of the 10 expected pts (pt1: cT4cN1 oropharyngeal; pt2: cT2 cN3 supraglottic squamous cell carcinoma) have been recruited and treated with SIB-IMRT with a curative intent.

Results: The RB model suggested a 6 week treatment with daily increasing dose/fractions as follows: PTV1: 1.70, 1.95, 2.15, 2.30, 2.35Gy; PTV2: 1.50, 1.75, 1.95, 2.05, 2.10Gy; PTV3: 1.40, 1.60, 1.80, 1.90, 1.95Gy. Both pts recruited in the FAMOSO protocol concluded the radiation treatment : pt1 with no change of the planned schedule; pt2 with interruption of MoAb-EGFr after the 5th administration and, consequently, the last 10 RT fractions of RT were administered with standard fractionation. The total dose to the PTV1 were 62.7 and 61.8 Gy, respectively. Maximun acute skin and mucosal toxicity was G3. With a follow up of 6 and 2 months, a partial response was obtained for pt1, while pt2 is still under evaluation.

Conclusion: New treatment strategies, even accelerated, are feasible when combining RT with radiosensitizing drugs. The RB model is adequate to set up the treatment provided radiobiological parameters are available from clinical data. The preliminary clinical data of the protocol FAMOSO give encouraging results, suggesting that the treatment schedule is feasible with acceptable acute toxicity. Longer follow up is needed to confirm toxicity findings and assess response rate, and of course more patients have to be studied.

EP-1720

Impact of contouring variability on tumour control and normal tissue toxicity in liver SBRT

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Purpose or Objective: Variability in the contouring of gross tumour and the derived planning target volumes (PTVs) between clinicians is well-known in radiotherapy. This study aims to quantify the impact of variability in contouring in terms of tumour control and normal tissue toxicity in Liver SBRT.

Material and Methods: The National Radiotherapy Trials Quality Assurance (RTTQA) Group planning benchmark case for the ABC07 Trial was used (addition of stereotactic body radiotherapy to systemic chemotherapy in locally advanced biliary tract cancers; CRUK A18752, sponsor University College London). 12 centers performed contouring independently using radiotherapy trial protocol as per RTTQA pre-trial QA process. Each centre applied margins to derive PTV as per local practice. A standardised Volumetric Modulated Arc Therapy (VMAT) plan was produced based on gold standard contours and applied to all 12 sets of submitted contours aiming to deliver 50Gy in 5 fractions. However, due to large GTV this was unavoidably de-escalated to 40Gy to meet trial mandatory mean non-GTV Liver constraint. Tumour control was assessed through biologically effective dose (BED) to 98, 95 and 90% of the gold standard PTV. 65Gy BED, although disappointingly low for SBRT, was considered